PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CANNING, Lewis, Reuben
Amersham plc
Amersham Laboratories
White Lion Road
Amersham
Buckinghamshire HP7 9LL
ROYAUME-UNI

Date of mailing (day/month/year)
29 January 2002 (29.01.02)

Applicant's or agent's file reference
PA9947-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/03374

International filing date (day/month/year)
01 September 2000 (01.09.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
NYCOMED AMERSHAM PLC
Amersham Laboratories
White Lion Road
Amersham
Buckinghamshire HP7 9LL
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.: +44 1494 545064
Facsimile No.: +44 1494 543977
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
AMERSHAM PLC
Amersham Laboratories
White Lion Road
Amersham
Buckinghamshire HP7 9LL
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.: +44 1494 545064
Facsimile No.: +44 1494 543977
Teleprinter No.:

3. Further observations, if necessary:
The agent's address has been changed accordingly.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Anman QIU

Telephone No.: (41-22) 338.83.38

Claims

1. A composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, characterised in that the radiopharmaceutical is a metal complex.

2. The composition of claim 1 where the radiopharmaceutical is a liquid or solution.

3. The composition of claims 1 or 2 where the metal of the metal complex is ^{111}In or ^{99m}Tc.

4. The composition of claims 1 to 3 where the silica coating is deposited by a PCVD process.

5. The composition of claims 1 to 4 where the container is a glass vial with a closure.

6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive ligand composition in a container which has a silica coating on the inner surface.

7. The kit of claim 6 where the metal complex is a ^{99m}Tc complex.

8. The kit of claims 6 or 7 where the non-radioactive ligand composition is lyophilised.

9. The kit of claims 6 to 8 where the silica coating is deposited by a PCVD process.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

CANNING, Lewis R.
NYCOMED AMERSHAM PLC
Amersham Laboratories
White Lion Road
Amersham, Bucks HP7 9LL
GRANDE BRETAGNE

DUE DATE:	N/A
FORMALITIES:	JHV
PAT. OFF:	LEC √F
ON DB:	21/12/01
CASE NO:	PA9947

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 17.12.2001
Applicant's or agent's file reference PA9947-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03374	01/09/2000	03/09/1999

Applicant
NYCOMED AMERSHAM PLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Senkel, H Tel.+49 89 2399-8071

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PA9947-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03374	01/09/2000	03/09/1999
International Patent Classification (IPC) or national classification and IPC A61K51/00		
Applicant NYCOMED AMERSHAM PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/03/2001	17.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hornich, E Telephone No. +49 89 2399 8721

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03374

I. Basis of the r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations
see separate sheet

SECTION V

1. *References*

D1: DE 198 01 861 A
D2: US-A-5 565 248
D3: DE 296 09 958 U1 was cited in the Application
D4: JP11-99192A was cited in the Application

1.1 **D1** discloses glass *containers* having an *internal coating* of e.g. SiO_2; the coating is prepared by e.g. *plasma enhanced chemical vapour deposition* (*PECVD*) and *prevents the leaching* of (metal)ions from the container-material into the (liquid) content (e.g. *pharmaceutical products*) (abstract; p. 2, l. 7f. and 12-25; p. 3, l. 66-68; p. 4, l. 3-6, l. 45-47, l. 67f.; p. 5, l. 8-33; claims 1, 2, 3, 6, 10, 11).

1.2 **D2** discloses plastic / metal *containers* having an *internal coating* of e.g. *silica*, which is *inert* to the packaged content (safe contact with e.g. food, beverages; desorption of packaging material components into the food is diminished; impermeability to polar and non-polar substances) (abstract; col. 1, l. 1-30; col. 2, l. 28-47; col. 5, l. 26-40; claim 1, 2).

1.3 **D3** discloses that glass containers having an *internal coating of* SiO_2 prepared by PCVD are useful for the storage of pharmaceutical or *diagnostic* solutions.

1.4 **D4**, according to the citation in the application, involves the storage of *radiopharmaceuticals* in *silica-coated vials*.

2. *Novelty* **(Art. 33(2) PCT)**

Compositions comprising a *radiopharmaceutical* in a *container* having a *silica coating on the inner surface* (the radiopharmaceutical being a ***metal complex***, claim 1) have not yet been disclosed in the available prior art.
A *kit* comprising a *non-radioactive organic ligand composition* in a container which

has a silica coating on the inner surface (claim 6) and compositions as defined in claims 10 and 11 have neither been described in the state of the art.

Novelty can therefore be **acknowledged** for the subject-matter of claims 1-14.

3. *Inventive Step* (**Art. 33(3) PCT**)

3.1 The *problem* to be solved, *derived from the description of the present application*, is that, when *radiopharmaceuticals,* namely *metal complexes, are stored in a container*, metal ions from the container-material are leached into the product, which may *adversely affect* the product (impurity, reactions of the metal with the radiopharmaceutical product; oligomerisation; promoting the co-precipitation of the product; toxicity and thus safety problems for products intended for human injection; biodistribution problems).

3.2 In his letter of 28/11/01 in response to the written opinion, the Applicant points out '*that the problem has been stated in a way which partly anticipates the solution by identifying that metal ions leached from the glass container are the source of the problem*'.

The Applicant contends that the problem would have to be formulated

> '*how to prevent intermittent impurity problems in radiopharmaceutical metal complex preparations pertaining to particulates in solution, batch to batch variability of unknown origin, and/or apparent loss of radioactive concentration*'.

The Applicant herewith emphasizes that the ***basis of the inventive step*** involved in present application is the ***formulation of the problem*** (identification of the source underlying the problem).

However, *interactions between the container material and the content of the container* represent a ***well-known problem***, and the *storage of pharmaceuticals* (or also food) in *inert containers* is a ***matter of routine*** *in order to prevent such interactions.* The skilled person would *regard inert containers as a matter of course* for the storage of (radio)pharmaceuticals.

Thus, assessment of inventive step cannot be based on the identification of the problem as being obvious to the skilled person.

3.3 In any case, the *solution* of the present application resides in a composition comprising a *radiopharmaceutical* (being a ***metal complex***) in a *container* which has a *silica coating on the inner surface*.

3.4 *Containers having an inert silica coating on the inner surface* (in order to prevent leaching of metal ions from the container-material) for the *safe storage* of *pharmaceuticals (e.g. diagnostics* (**D3**), *radiopharmaceuticals* (**D4**)), food and beverages, however, have *already been disclosed* in the prior art (see above-cited **D1** and **D2**; citations in the application on p. 1 and 2, e.g. *DE 29609958U1=**D3*** and *JP 11-99192A*=**D4**), thus *already providing a solution* for the problem underlying the present application.

The storage of specific radiopharmaceuticals, namely *metal complexes* in silica-coated containers in order to *prevent the adverse affection* of the pharmaceuticals can be derived from the prior art (no unexpected effect) and thus only represents a *further possible use* of the *already known containers*.

3.5 Thus, an **inventive step** can presently **not be acknowledged** for the subject-matter of claims 1-14.

4. *Industrial Applicability* **(Art. 33(4) PCT)**

The requirements of industrial applicability are **fulfilled** for claims 1-14.

12

PATENT COOPERATION TREATY

PCT

REC'D 19 DEC 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PA9947-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
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International Patent Classification (IPC) or national classification and IPC A61K51/00		
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Date of submission of the demand	Date of completion of this report
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Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hornich, E Telephone No. +49 89 2399 8721

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03374

I. Basis of the report

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	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations
see separate sheet

SECTION V

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A *kit* comprising a *non-radioactive organic ligand composition* in a container which

has a silica coating on the inner surface (claim 6) and compositions as defined in claims 10 and 11 have neither been described in the state of the art.

Novelty can therefore be **acknowledged** for the subject-matter of claims 1-14.

3. *Inventive Step* **(Art. 33(3) PCT)**

3.1 The *problem* to be solved, *derived from the description of the present application*, is that, when *radiopharmaceuticals,* namely *metal complexes, are stored in a container*, metal ions from the container-material are leached into the product, which may *adversely affect* the product (impurity, reactions of the metal with the radiopharmaceutical product; oligomerisation; promoting the co-precipitation of the product; toxicity and thus safety problems for products intended for human injection; biodistribution problems).

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The Applicant contends that the problem would have to be formulated

> '*how to prevent intermittent impurity problems in radiopharmaceutical metal complex preparations pertaining to particulates in solution, batch to batch variability of unknown origin, and/or apparent loss of radioactive concentration*'.

The Applicant herewith emphasizes that the ***basis of the inventive step*** involved in present application is the ***formulation of the problem*** (identification of the source underlying the problem).

However, *interactions between the container material and the content of the container* represent a ***well-known problem***, and the *storage of pharmaceuticals* (or also food) in *inert containers* is a ***matter of routine*** *in order to prevent such interactions.* The skilled person would *regard inert containers as a matter of course* for the storage of (radio)pharmaceuticals.

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3.3 In any case, the *solution* of the present application resides in a composition comprising a *radiopharmaceutical* (being a ***metal complex***) in a *container* which has a *silica coating on the inner surface*.

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The storage of specific radiopharmaceuticals, namely *metal complexes* in silica-coated containers in order to *prevent the adverse affection* of the pharmaceuticals can be derived from the prior art (no unexpected effect) and thus only represents a *further possible use* of the *already known containers*.

3.5 Thus, an **inventive step** can presently **not be acknowledged** for the subject-matter of claims 1-14.

4. *Industrial Applicability* **(Art. 33(4) PCT)**

The requirements of industrial applicability are **fulfilled** for claims 1-14.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 00/03374

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K51/12 A61K51/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C03C C23C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 565 248 A (PLESTER GEORGE ET AL) 15 October 1996 (1996-10-15) abstract column 2, line 25-35 column 5, line 25-40 ≠10953	1,2,4-6, 9-11,14
A	WO 96 26163 A (ELF ATOCHEM VLISSINGEN BV ;HOEKMAN LEENDERT CORNELIS (NL); CARSON) 29 August 1996 (1996-08-29) abstract; claim 13 ≠10854	1,2,4-6, 9-11,14
X	DE 198 01 861 A (SCHOTT GLAS) 22 July 1999 (1999-07-22) abstract ≡ US 6200658 ≠10854	1,2,4-6, 9-11,14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2001	27/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5565248 A	15-10-1996	BR 9505647 A	16-01-1996
		EP 0693137 A	24-01-1996
		JP 8508964 T	24-09-1996
		NO 954008 A	09-10-1995
		WO 9521948 A	17-08-1995
		ZA 9501047 A	02-05-1996
WO 9626163 A	29-08-1996	AU 4849096 A	11-09-1996
		BR 9607269 A	15-12-1998
		CA 2211940 A	29-08-1996
		CN 1175935 A	11-03-1998
		CZ 9702604 A	14-01-1998
		EP 0810980 A	10-12-1997
		HU 9801366 A	28-08-1998
		JP 11504610 T	27-04-1999
		NO 973829 A	20-08-1997
		NZ 302437 A	27-04-1998
		PL 321863 A	22-12-1997
		TR 9700841 T	21-02-1998
		ZA 9601390 A	16-07-1996
DE 19801861 A	22-07-1999	FR 2773796 A	23-07-1999
		IT T0990035 A	20-07-1999
		JP 11278868 A	12-10-1999
		US 6200658 B	13-03-2001

(51) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17569 A2

(51) International Patent Classification[7]: A61K 51/00

(21) International Application Number: PCT/GB00/03374

(22) International Filing Date:
1 September 2000 (01.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9920772.2 3 September 1999 (03.09.1999) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/17569 A2

(54) Title: IMPROVED CONTAINER COMPOSITION FOR RADIOPHARMACEUTICAL AGENTS

(57) Abstract: The present invention relates to improved radiopharmaceutical metal complex compositions, comprising the radiopharmaceutical metal complex in a container, where the container has an internal coating of SiO_2. The internal coating of SiO_2 is preferably deposited by a plasma chemical vapour deposition (PCVD) process. Non-radioactive kit compositions for the preparation of radiopharmaceutical metal complexes using the containers of the present invention are also described.

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17569 A3

(51) International Patent Classification[7]: A61K 51/12, 51/04

(21) International Application Number: PCT/GB00/03374

(22) International Filing Date:
1 September 2000 (01.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9920772.2 3 September 1999 (03.09.1999) GB

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
15 November 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/17569 A3

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Improved Container Composition for Radiopharmaceutical Agents

Summary of the Invention

The present invention relates to improved containers for radiopharmaceutical metal complexes, where the container has an internal coating of silica (ie. silicon dioxide or SiO_2), preferably deposited by a plasma chemical vapour deposition (PCVD) process.

Field of the Invention

The present invention relates to radiopharmaceutical metal complexes, and kits for the preparation of such complexes, in a container having a silica coating on the surface(s) which are in contact with the radiopharmaceutical.

Background to the Invention

US 4385086 (1983) discloses that a variety of materials (eg. soda glass, ceramics and metals) can be coated with highly oxidised silicon to prevent the leaching of metal ions from the material.

FR 2697014 A1 (1994) discloses the silica coating of bottles, flasks, ampoules and other containers intended for use with food or liquid pharmaceutical products, to reduce leaching of metals from the container into the liquid contents of the container.

DE 29609958 U1 discloses that glass containers having an internal coating of SiO_2 prepared by PCVD are useful for the storage of pharmaceutical or diagnostic solutions.

JP 11-99192A discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as ^{201}Tl solution to the surface of the glass. The silica coating of these vials is manufactured by the method described in JP 2815595 B which involves treating the glass surface with a silyl tetraisocyanate vapour in a carrier gas, followed by heating at high temperatures. JP 2815595 B also discloses that such a silica coating is useful to prevent leaching of impurities such as alkali from the glass into medical products.

Summary of the Invention

The present invention relates to silica-coated containers in combination with the following categories of products:

(i) radioactive radiopharmaceutical products which are metal complexes,

(ii) lyophilised non-radioactive kits for the preparation of radiopharmaceutical metal complexes, especially for the preparation of ^{99m}Tc radiopharmaceuticals.

Detailed Description of the Invention

The present invention relates to a composition comprising a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. The present invention also relates to non-radioactive, preferably lyophilised kits for the preparation of radiopharmaceutical metal complexes, where the kit composition is supplied in a container which has a silica coating on the inner surface.

Suitable silica-coated containers for use in the present invention are commercially available, e.g. a silica-coated vial called Silicoat is available from Fuji Glass KK, and a silica-coated vial called Type I Plus is available from Schott Glas. The Type I Plus vial is prepared by a plasma chemical vapour deposition (PCVD) process.

Other containers can be coated with silica using known methods, where the silicon-containing layer is deposited from either gas phase or liquid phase contact with the container surface(s), with optional pyrolysis and/or oxidation to convert the deposited silicon-containing layer to SiO_2. Such methods are known in the art. Using either approach, irregularly-shaped containers can be coated. Examples of gas phase deposition are PCVD, and the process of JP 2815595 B which uses silyl tetraisocyanate vapour in carrier gas. The latter process delivers the silicon-containing layer in a single step, with pyrolysis of silyl tetraisocyanate required to give the final product, i.e. the coated vial. Depending on the efficiency of the heat transfer, the coating layer may not be pure SiO_2, but perhaps contain carbon or nitrogen. The silica-coated vial prepared by PCVD has advantages over the disclosures of JP 2815595 B and JP 11-99192A, because the SiO_2 layer prepared by PCVD is in fact developed by multiple exposure to the vapour phase silicon reagent. The result is a much more uniform layer of high purity SiO_2, which is mechanically sound and resistant to abrasion etc. Hence PCVD is a preferred process for use in containers of the present invention.

The term "metal complex" as used herein means a coordination complex of a metal (M) with an organic ligand (L). This is to be contrasted with an uncomplexed or free metal ion e.g. the monovalent thallium cation Tl^+. The term 'organic ligand' as used herein means a carbon-containing compound which comprises at least one heteroatom suitable for

coordination to a metal, such as N, O, S, P or Se, or combinations thereof. Examples of organic ligands are amines, hydrazines (eg. hydrazinonicotinamide or HYNIC), ethers such as crown ethers, thiols or thioethers, oximes, isonitriles (eg. sestamibi), phosphines, amides, pyridines or other heterocyclic molecules such as quinolines. Multiple metal donor atoms can be arranged together to form chelating agents or polydentate ligands such as:

- diaminedioximes such as propyleneamineoxime (ie. PnAO), or hexamethylpropyleneamineoxime (ie. HMPAO), or analogues thereof;
- hydroxyquinolines;
- N2S2 ligands such as diaminedithiols (eg. ethylcysteineate dimer or ECD, ie. bicisate), diamidedithiols or amideaminedithiols;
- N3S ligands such as thioltriamides (eg. mercaptoacetyltriglycine or MAG3);
- diphosphines (eg. tetrofosmin);
- dithiols (eg. dimercaptosuccinic acid or DMSA);
- aminocarboxylate ligands (eg. EDTA or DTPA);

and many more combinations as are well known in the art.

If leached metal ions M' (such as aluminium or sodium), leach from glass into a chemical product which is a radiopharmaceutical metal complex of a radiometal M, these leached metal ions may adversely affect the product in a manner which goes beyond the simple presence of M' as an impurity:

(i) $ML_n + M' \rightarrow M'L_q + M$ ligand exchange or transmetallation

(ii) $L + M' \rightarrow M'L_q$ complexation

where:

M is the radiometal of the desired radiopharmaceutical product,

L is the organic ligand;

M' is the leached metal ion;

ML_n is the metal complex radiopharmaceutical product, which may comprise 2 or more different organic ligands L;

n is number of ligands (L) attached to M and is an integer of value 1 to 8;

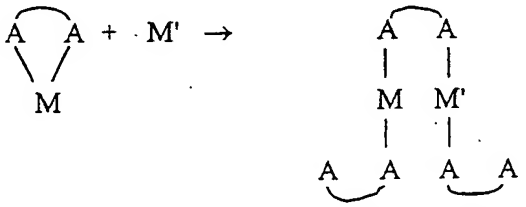
$M'L_q$ is the metal complex impurity;

q is number of ligands (L) attached to M' and is an integer of value 1 to 8.

Process (i) can occur when the leached metal or metals (M') have greater affinity for one or more of the organic ligands (L) than the radiometal (M) of the radiopharmaceutical product. For a radioactive product, ML_n is the radiopharmaceutical and could be e.g. $^{111}In(oxine)_3$ where M is ^{111}In and oxine is 8-hydroxyquinoline, or the ^{99m}Tc complex of DMSA (dimercaptosuccinic acid). It is important to recognise that, for radiopharmaceutical products, ML_n is present at extremely low (typically nanomolar or picomolar) concentrations. Consequently, even low levels of leached metal ions (M') from the glass, can have a significant effect on the radiochemical purity of the ML_n product, by increasing the levels of free radiometal (M) impurity. Such free radiometal could then generate further radioactive impurities by undergoing e.g. redox reactions, or complexation with other available ligands.

In addition to, or instead of equation (i), complexation (ii) may also occur. This leads to the presence of undesirable $M'L_q$ impurities in the product ML_n. $M'L_q$ is non-radioactive, but for a radiopharmaceutical agent, the ligand (L) is usually present in vast chemical excess over the metal (M) present, hence if M' has any affinity for L, equation (ii) is always likely to occur. $M'L_q$ may be insoluble in the medium present in the radiopharmaceutical vial or container, and may thus tend to precipitate. This may potentially promote co-precipitation of the desired species ML_n, and hence introduce yet further potential radioactive impurities.

When L is a multidentate ligand, such as a chelating agent the number of metal donor sites (A) per ligand (L) may be 2, 3, 4, 5, 6 or 8 typically. In that case, a process which is a special case of equation (i) above could occur as follows:

(iii) 

where: the free A donors can complex to further M/ M' atoms etc.

note: the curved lines represent the chain of atoms linking the A groups.

leading to dimeric or oligomeric binuclear or polynuclear metal complexes involving both radiometal M and non-radioactive metal M'. The leached metal (M') may be less amenable to chelation by polydentate ligand (L), and hence favour such polynuclear species, even when M does not. This would result when the energetics are less favourable, e.g. M' is too small for two A groups to coordinate without undue steric interactions from either the A

groups themselves, or the ligand backbone linking the A groups. Clearly, the greater the denticity of the ligand L (i.e. the greater the number of A metal donor sites), the greater the potential complexity of the impurity product.

In the light of the above, it can be seen that the influence of leachable metal ions (M'), can have effects which go far beyond just the presence of M' as a metal ion impurity. This is important for radiopharmaceutical metal complex products and is not recognised by JP 11-99192A, which makes no specific reference to radiopharmaceuticals which are metal complexes. The ^{201}Tl radioisotope taught by JP 11-99192 A is an uncomplexed radiometal in the chemical form of the Tl(I) cation Tl^+. The teaching of JP 11-99192 A relates only to adsorption effects *via* an ion exchange mechanism for the Tl-201 cation (ie. Tl^+) with the non-radioactive Na^+ and K^+ ions of the glass container walls. The main thrust of JP 11-99192 A is to a radiopharmaceutical vial having reversed text characters on the surface of the container

For uncoated glass containers, the leaching of metal ions from the glass can potentially be overcome, or at least reduced, by washing with dilute aqueous acid solutions (to remove relatively labile leachable metal ions), following by rinsing and (optionally) drying steps, before the container is charged with product. The layer of silica (SiO_2) suppresses any such leaching of metal ions (M'), and hence obviates the need for any such washing steps. This simplification is particularly important for diagnostic products intended for human use such as radiopharmaceuticals, which are typically administered by injection into the human bloodstream, since these washing steps must be done in a sterile manner. Hence although such steps may be straightforward, their removal represents a significant improvement.

The radiopharmaceutical product ^{111}In-oxine aqueous solution has been observed to suffer from an intermittent problem whereby, in some batches ^{111}In activity is lost to an insoluble precipitate which settles out of solution. Model experiments have identified this precipitate as a mixture of aluminium oxinate, with co-precipitated $^{111}In(oxine)_3$ (see Example 2). This illustrates the fact that the leaching of metal ions, in that case aluminium, from glass can cause unforeseen problems for metal complex radiopharmaceuticals, even when the initial effect is simply to form a $M'L_q$ complex as per equation (ii) above. It will be recognised that the interaction of leached metal ions with radiopharmaceutical metal complexes at tracer concentrations could produce a variety of impurities which are difficult to predict, identify and control when the glass can function as an uncontrolled source of a variety of metal ion impurities. Consequently, elimination of the leached metal ion by use of an inert barrier layer of SiO_2 eliminates the cause of this problem. Example 1 shows that a silica-coated vial reduces the leaching of aluminium to minimal levels, and hence solves the problem referred to above for $^{111}In(oxine)_3$.

Similarly, a lyophilised non-radioactive kit for the preparation of the kidney imaging agent ^{99m}Tc-DMSA has been found to suffer from problems of radioactive particulate impurities following reconstitution with ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$). The particle size of these radioactive particles is such that, once administered to the patient, the particles are retained in the liver. This represents a major problem for an agent which is intended to be used for kidney imaging. Example 4 shows that this biodistribution problem occurs when higher concentrations of aluminium ions than normal are present. Hence eliminating the leaching of aluminium from the glass vial is expected to significantly reduce or eliminate this problem. The problem with ^{99m}Tc-DMSA indicates

that leaching can occur even in lyophilised products which are reconstituted to give the radiopharmaceutical, i.e. that leaching can occur even when the contact time of the solution with the glass is only a matter of minutes.

JP 11-99192A concerns itself only with the issue of whether a free radioactive metal ion, (^{201}Tl as Tl^{+}), is adsorbed onto the vial walls. For a radiopharmaceutical metal complex (ML_n), the non-radioactive organic ligand L and its complex $M'L_q$ may suffer from adsorption problems. L may also potentially complex with M' ions which remain bound within the container walls to form $M'L_q$ complexes chemically bound to the glass. Adsorption is particularly likely to be a problem when L and/or $M'L_q$ is not too soluble in the solution medium, e.g. a lipophilic ligand such as oxine in a predominantly aqueous medium. Such loss of ligand due to adsorption or complexation may not adversely affect the preparation of the metal complex (ML_n) *per se*, since for a radiopharmaceutical L is usually present in vast chemical excess over M. Unwarranted loss of L does, however, impact on the reproducibility of manufacture of a controlled diagnostic product for human administration, since variable assay results for L are highly undesirable with respect to GMP. Example 3 demonstrates oxine ligand loss problems for an oxine ligand aqueous solution formulation, and shows that loss of oxine can occur by both the mechanisms referred to above. Silica-coated vials would eliminate loss of oxine to aluminium, and would be expected to reduce the degree of adsorption. The overall effect would be a reduction in the loss of oxine ligand from the solution. Hence, for these reasons also, metal complex radiopharmaceuticals in silica-coated vials have surprising advantages compared to what is described in the prior art.

The silica-coated vial can be used in combination with other non-radioactive components of a kit for the preparation of metal complex radiopharmaceuticals apart from the organic ligand (L), e.g. stabilisers, or bacteriostats. Such stabilisers or bacteriostats may suffer from analogous problems to those described above for oxine – ie. potential adsorption and/or complexation with leached metals. Bacteriostats include parabens, benzyl alcohol, cetrimide, benzoic acid, chlorbutanol, chlorocresol, cresol, phenol, benzethonium chloride and thiomersal. Some bacteriostats such as methyl paraben (ie. methyl *p*-hydroxybenzoate), or propyl paraben (propyl *p*-hydroxybenzoate) are relatively insoluble in water, and hence a silica-coated container would be expected to reduce formulation problems. Also, cobalt is known as a stabiliser for the ^{99m}Tc metal complex of the ligand HMPAO (hexamethylpropyleneamine oxime) [Eur. J. Nucl. Med., 20, 661-6 (1993) P. S. Weisner *et al*], and may be supplied in a separate vial to the HMPAO ligand vial. Reduced adsorption of cobalt onto the vial walls of a silica-coated vial is shown in Example 5. This shows that adsorption can occur in macroscopic amounts, not just at the tracer concentration described in the prior art for ^{201}Tl, and that silica-coated containers are useful for excipients used in the preparation of metal complex radiopharmaceuticals, such as stabilisers or bacteriostats.

Experimental

Example 1

Groups of 10 Type I Plus vials (Schott Glas) were subjected to a series of stress tests to demonstrate the robustness of the silica coating with respect to leachable ions.

The basic test was the resistance of the coating to the leaching of cations when autoclaved with 0.04M aqueous HCl. This test was performed after vials were exposed to the following stress test conditions 1 to 4:

1. Vials were washed, and then pyrogen baked. 2ml of 0.04M HCl was added and the vials sealed. Test vials were autoclaved, then stored upright at 40°C before testing for leachable cations.
2. Vials were stored for 6 weeks at -196°C, then washed and pyrogen baked. 2ml of 0.04M HCl was added to each vial, and the vials were then sealed, autoclaved and tested for leachable cations.
3. As test 2, except that the vials were stored at -70°C, -20°C, +20°C and +40°C/75% relative humidity.
4. Further tests included vials pyrogen baked 3 times, vials containing 0.04M HCl autoclaved three times, vials gamma irradiated (35.4 – 36.2 kGy dose).

All test solutions were measured by ICP for silicon, sodium, aluminium and boron, ie. those cations considered to be most leachable from the vial surface. The results are given in Table 1.

Table 1

Test Number		Si	Na	Al	B
1		0.149	Nd	0.006	Nd
2		0.163	Nd	Nd	Nd
3	-70°C	0.167	Nd	Nd	Nd
	-20°C	0.193	0.005	0.002	0.002
	+20°C	0.193	0.009	0.005	0.003
	+40°C	0.236	0.006	0.002	0.002
4	bake	0.110	Nd	0.010	Nd
	X3	0.378	0.012	Nd	0.006
	Gamma	0.102	0.003	Nd	Nd

Note: each table entry is the mean of 12 batch runs, each batch of 10 vials (i.e. 120 vials tested), expressed in $\mu g/cm^3$ of test solution.

Nd = not detected. Detection limits (in $\mu g/cm^3$):

Si – 0.003

Na – 0.004

Al – 0.004

B – 0.004

All of the results were satisfactory, particularly for the key cations sodium and aluminium, each of which had mean values of approximately 0.01μg per ml of test solution. These very low levels demonstrate the robustness of the silica coating under stress conditions.

There were no significant differences in the results obtained between vials from different proving runs. This demonstrates the reproducibility of the silica coating process.

Example 2: Indium Oxine and Aluminium

A non-radioactive oxine stock solution without ^{111}In was prepared from approved reagents. The active sub-batch was prepared from the same reagents but with sufficient ^{111}In-indium chloride in 0.04 M HCl stock solution to give a reference activity of 0.1 mCi/ml.

For the active experiment, 10 P6 glass vials (ie. uncoated USP Type 1 glass vials) were each dispensed with 1 ml of radioactive stock solution. For the inactive experiment, approximately 390 P6 vials were each dispensed with 1 ml of oxine stock solution. All the vials were stoppered, oversealed and autoclaved in the approved manner. The active vials were subjected to RAC (radioactive concentration) determination, both initially and after standing for 1 day. The inactive vials were left for 3 days in the upright position.

The precipitate was harvested from the inactive P6 vials by the following procedure:

10 vials were decapped and decanted into a Sterilin container;

each vial was washed with 1 ml pyrogen-free water and the washings added to the Sterilin;

a further 10 vials were treated as above to create a second filled Sterilin;

the Sterilins were centrifuged at 2000 rpm for 10 minutes;

the supernatants were decanted and the above procedures repeated using the same Sterilin containers;

this cycle was repeated until all the inactive vial contents had been processed through the two Sterilins;

the precipitate in each Sterilin were transferred to separate tared vials and freeze-dried;

at the completion of freeze-drying, the vials were re-weighed.

Results:

(i) Active vials

The P6 vials gave a mean decrease in of ^{111}In activity of 16.7% with a maximum of 38.7%. However, some of the P6 vials had initial RACs substantially below the expected value of 0.1 mCi/ml. The vials with the lower initial RACs tended subsequently to show the highest RAC drops.

(ii) Inactive vials

The processing of the inactive vials yielded a small but visible quantity of green precipitate in each Sterilin. The total yield of freeze-dried precipitate was 7.0 mg. ^{1}H NMR and chromatographic analysis compared with an authentic sample of aluminium oxinate showed the precipitate to be predominantly aluminium oxinate.

Example 3: Oxine Ligand Loss

20 P6 glass vials were rinsed with water, drained and baked to depyrogenate. Each vial was then dispensed with an aqueous solution containing 50 μg of oxine, and the oxine content determined by HPLC at various time points. The results are shown in Table 2:

Table 2: Oxine Loss by HPLC

Time Point	Oxine in Solution	Solution/ Suspension Al(ox)3	Glass oxine	Glass Al(ox)3	Recovery (%)
initial	25.2	8.5	5.1	2.3	82
reference	20.1	26.7	3.1	6.0	~100
expiry	20.3	27.7	2.5	7.3	~100
expiry +14 days	19.0	16.4	6.6	5.7	95

HPLC System

Column: Hamilton PRP1, 150 x 4.1mm, μm particle size

Eluent A: 25 mM KH_2PO_4 adjusted to pH 10.3 – 10.5 with KOH

Eluent B: Acetonitrile

Gradient: $0\%\ B \xrightarrow{15\ min} 50\%\ B \xrightarrow{5\ min} 50\%\ B \xrightarrow{3\ min} 0\%\ B$

Flow Rate: 1.75ml/min.

Injection volume: 20μg

Detection: UV at 254nm, path length 10mm

System control and data processing: Gilson 715 System Controller

The system was calibrated using 50 μg/ml solutions of oxine in water and aluminium oxinate in acetonitrile. Retention time of oxine was ca. 15 – 15.2 min, and Al(oxinate) ca. 17 min.

For solution/suspension measurements, samples of vial contents were taken directly and injected. The oxine and aluminium oxinate peaks were each integrated and the aluminium oxinate peak area normalised to give an oxine equivalent. The results were then scaled to give a total solution/suspension content. For measurements of oxine and aluminium oxinate adsorbed on the vial walls, the vial was decapped, drained and carefully rinsed with 0.2ml acetonitrile. 20 μg of the rinse solution was injected, the peaks integrated and the aluminium oxinate peak area normalised to give an oxine equivalent. Previous experiments had shown oxine losses to the vial stopper to be negligible.

Example 4

Freeze-dried kits using USP Type 1 glass vials (i.e. P6 uncoated vials) containing the following formulation were prepared:

meso–DMSA	1.0mg
$SnCl_2.2H_2O$	0.42mg
ascorbic acid	0.7mg
inositol	50.0mg

These vials were reconstituted with 0.9% saline B.P. and set aside for 1 hour. A proportion (ca. 1 in 10) of the vials were found to contain aluminium levels of up to 2 μg/vial. Standing these vials for longer periods gave levels of up to 6 μg/vial of aluminium.

When the above lyophilised DMSA kit formulation vials were reconstituted with ^{99m}Tc generator eluate (ie. ^{99m}Tc-pertechnetate in saline) which was known to contain 1μg/ml aluminium ion, the product exhibited atypical elevated liver uptake in a rat biodistribution test. The atypical behaviour was reflected in reduced kidney: liver and

spleen ratios in the range 5.9 to 7.7 at 4 hours post injection. In contrast, kits reconstituted with normal ^{99m}Tc generator eluate give ratios of 13 to 20:1, i.e. significantly higher. Leached aluminium can thus be linked to poor product performance for a significant proportion of vials.

Example 5

A 100μg/ml solution of $CoCl_2.6H_2O$ was prepared by dissolving 0.100g $CoCl_2.6H_2O$ in water in a 1000ml volumetric flask and making up to volume. 2.0cm^3 portions of this solution were immediately dispensed into 6 of each of the following types of vials:

P6 standard glass,

Schott Type 1 Plus (silica-coated),

the vials were autoclaved, then allowed to cool, and the cobalt content assayed by UV. The results are given in Table 3, which includes values for the cobalt stock solutions for comparison.

Table 3: Cobalt Adsorption

Vial	Vol added (cm^3)	Cobalt content ($\mu g/cm^3$)	Statistics
Stock ≠1	1.997	24.58	
≠2	1.998	24.41	mean = 24.31
≠3	1.998	24.32	max = 24.58
≠4	1.999	24.58	min = 23.97
≠5	1.992	23.97	
≠6	1.995	24.03	
P6 ≠1	1.976	13.87	
≠2	1.982	13.27	mean = 14.61
≠3	1.985	16.52	max = 17.84
≠4	1.978	17.84	min = 12.80
≠5	1.982	13.40	
≠6	1.985	12.80	
coated ≠1	1.986	25.21	
≠2	1.975	24.86	mean = 24.49
≠3	1.979	23.81	max = 25.21
≠4	1.983	24.82	min = 23.81
≠5	1.987	24.40	
≠6	1.983	23.87	

Claims

1. A composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, characterised in that the radiopharmaceutical is a metal complex.

2. The composition of claim 1 where the radiopharmaceutical is a liquid or solution.

3. The composition of claims 1 or 2 where the metal of the metal complex is ^{111}In or ^{99m}Tc.

4. The composition of claims 1 to 3 where the silica coating is deposited by a PCVD process.

5. The composition of claims 1 to 4 where the container is a glass vial with a closure.

6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

7. The kit of claim 6 where the metal complex is a ^{99m}Tc complex.

8. The kit of claims 6 or 7 where the non-radioactive organic ligand composition is lyophilised.

9. The kit of claims 6 to 8 where the silica coating is deposited by a PCVD process.

10. A composition for the preparation of a stabilised radiopharmaceutical metal complex which comprises a stabiliser suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

11. A composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

12. The composition of claim 11, where the bacteriostat comprises a paraben.

13. The composition of claims 10 to 12, where the metal of the metal complex is ^{111}In or ^{99m}Tc.

14. The composition of claims 10 to 13, where the silica coating is deposited by a PCVD process

PATENT COOPERATIC TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 May 2001 (22.05.01)	
International application No. PCT/GB00/03374	**Applicant's or agent's file reference** PA9947-PCT
International filing date (day/month/year) 01 September 2000 (01.09.00)	**Priority date** (day/month/year) 03 September 1999 (03.09.99)
Applicant GILL, Stephen et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 March 2001 (12.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 00/03374

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K51/12 A61K51/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C03C C23C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 565 248 A (PLESTER GEORGE ET AL) 15 October 1996 (1996-10-15) abstract column 2, line 25-35 column 5, line 25-40	1,2,4-6, 9-11,14
A	WO 96 26163 A (ELF ATOCHEM VLISSINGEN BV ;HOEKMAN LEENDERT CORNELIS (NL); CARSON) 29 August 1996 (1996-08-29) abstract; claim 13	1,2,4-6, 9-11,14
X	DE 198 01 861 A (SCHOTT GLAS) 22 July 1999 (1999-07-22) abstract	1,2,4-6, 9-11,14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2001	27/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/GB 00/03374

Patent document cited in search r port	Publication date	Patent family member(s)	Publication date
US 5565248 A	15-10-1996	BR 9505647 A	16-01-1996
		EP 0693137 A	24-01-1996
		JP 8508964 T	24-09-1996
		NO 954008 A	09-10-1995
		WO 9521948 A	17-08-1995
		ZA 9501047 A	02-05-1996
WO 9626163 A	29-08-1996	AU 4849096 A	11-09-1996
		BR 9607269 A	15-12-1998
		CA 2211940 A	29-08-1996
		CN 1175935 A	11-03-1998
		CZ 9702604 A	14-01-1998
		EP 0810980 A	10-12-1997
		HU 9801366 A	28-08-1998
		JP 11504610 T	27-04-1999
		NO 973829 A	20-08-1997
		NZ 302437 A	27-04-1998
		PL 321863 A	22-12-1997
		TR 9700841 T	21-02-1998
		ZA 9601390 A	16-07-1996
DE 19801861 A	22-07-1999	FR 2773796 A	23-07-1999
		IT T0990035 A	20-07-1999
		JP 11278868 A	12-10-1999
		US 6200658 B	13-03-2001

PATENT COOPERATI TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PA9947-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 03374	01/09/2000	03/09/1999
Applicant		
NYCOMED AMERSHAM PLC		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/03374

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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